PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

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19 APR 2004
CARPMAELS & RANSFORD
ACTIONED

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	14.04.2004
Applicant's or agent's file reference	**IMPORTANT NOTIFICATION**
P029441WO	

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB 03/00211	21.01.2003	22.01.2002

Applicant
EUROPEAN MOLECULAR BIOLOGY LABORATORY et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Büchler, S Tel. +49 89 2399-8090

Form PCT/IPEA/416 (January 2004)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P029441WO	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/GB 03/00211	International filing date *(day/month/year)* 21.01.2003	Priority date *(day/month/year)* 22.01.2002

International Patent Classification (IPC) or both national classification and IPC
C12N9/12

Applicant
EUROPEAN MOLECULAR BIOLOGY LABORATORY et al.

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
21.08.2003	14.04.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Valcarcel, R Telephone No. +49 89 2399-2368

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB 03/00211

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-46 as originally filed

Claims, Numbers

1-54 as originally filed

Drawings, Sheets

1/10-10/10 as originally filed

Sequence listing part of the description, pages:

8, filed with the letter of 22-04-2003,

2. With regard to the **language,** all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☒ furnished subsequently to this Authority in written form.
- ☒ furnished subsequently to this Authority in computer readable form.
- ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 28-30 (all entirely); 31,33-38 (all partially); 36-38,40 (with respect to industrial applicability)

   because:

   ☒ the said international application, or the said claims Nos. 36-38,40 (with respect to industrial applicability) relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 28-30 (all entirely); 31,33-38 (all partially)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees, the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

☐ complied with.

☒ not complied with for the following reasons:

see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☒ all parts.

☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	27,43,45-47,49-51,53,54
	No: Claims	1-26,31-42,44,48,52
Inventive step (IS)	Yes: Claims	NONE
	No: Claims	1-27,31-54
Industrial applicability (IA)	Yes: Claims	1-27,31-35,39,41-54
	No: Claims	NONE

2. Citations and explanations

see separate sheet

Re Item III

According to Rule 66.1(e) PCT, claims relating to inventions in respect of which no international search report (ISR) has been established need not be the subject of international preliminary examination. As the subject-matter of claims 28-30 (all entirely) and 31, and 33-38 (all partially) has not been searched (see BOX I of the International Search Report), no preliminary examination has been carried out for these claims.

Claims 36-38 and 40 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item IV

The application lacks unity contradicting Rule 13 PCT. Rule 13 PCT states that for unity of invention to be present, all subject-matter should be linked by a single general inventive concept. The only common concept linking the two recognized inventions in the present application (see lack of unity section in the ISR) is the fact that a protease cleavage site is located near the boundary of the "cap" region and the SH3 domain. This concept is not considered as an inventive concept since it is neither novel nor inventive. A site recognized by a protease is very likely to be present in N-terminal locations of existing c-Abl proteins.

Many proteases are known, and under certain conditions they might cleave specifically or unspecifically at different locations of a protein. Thus, it is considered that any c-Abl or c-Abl mutant which might be cleaved at his N-terminus under certain conditions, would fall under the scope of claim 42, even the wild type c-Abl. Thus, such c-Abl proteins would not be necessarily related to invention 1. Since no other feature could be identified neither in the description nor in the claims that could be considered a "special" technical feature in the sense of Rule 13.2 PCT, each invention must be regarded as a separate potential invention. However, the IPEA has elected to carry out examination on the subject-matter of all claims.

Re Item V

1. The document numbering corresponds to the order of citation in the search report.
2. This communication is based on the assumption that all claims enjoy priority rights

from the filing date of the priority document. If it later turns out that this is not correct, the document D1 cited in the international search report would become relevant.

3. Claims 41 and 52 refer to a transgenic animal, which includes transgenic humans. The Applicant is suggested to exclude transgenic humans.

4. The IPEA considers that the identification of the "cap region" of Abl as an inhibitor of the Abl tyrosine kinase activity, involves an inventive step. Although, in the prior art there were suggestions that an intramolecular interaction in c-Abl could be responsible for such inhibition (see e.g. page 1514, left column, third paragraph of D7; or page 282, left column of D6), there is no indication in the prior art to the fact that the cap region would be responsible for a tyrosine kinase inhibition. Furthermore, although the skilled person could have discovered the effect of the "cap region" by using standard methods in the art, there is no indication that he would have done so.

5. However, the present set of claims does not meet the requirements of the PCT for the following reasons:

Lack of novelty

5.1 **Claims 1-26, and 31-41 not only refer to the cap region but to a "functional equivalent"** thereof. As no precise definition is given for such an expression, any compound which inhibits the Abl tyrosine kinase has been considered as a functional equivalent and thus, the subject-matter of claims 1-26, and 31-41 is considered as not novel, contravening the requirements of Article 33(2) PCT.

As examples D3, D4 or D5 disclose Abl protein kinase inhibitors, which are considered as functional equivalents of the cap region of c-Abl as far as there is no precise definition for such an expression. These documents also disclose the use of such tyrosine kinase modulators in therapy (see e.g. D3, corresponding to a patent application from the same Applicant as the present application).

5.2 **The subject-matter of claims 42, 44, 48, and 52 is also not novel.** A given protease under certain conditions might cleave at different locations of a protein, and thus, any c-Abl or c-Abl mutant which might be cleaved at his N-terminus under certain conditions, would fall under the scope of these claims, **even the wild type c-Abl** (for transgenic animals see e.g. page 181 of D2, left column, first two

paragraphs).

Insufficient disclosure, lack of inventive step

5.3 **Claims 1-27, and 31-54** do not meet the requirements of Articles 6 PCT and Article 33(3) PCT, since the subject-matter of these claims **is not sufficiently disclosed and it does not involve an inventive step.**

The present application discloses the inhibition of c-Abl in vitro by using the N-terminal region of c-Abl (cap region). There is no sufficient evidence for the fact that such region would act as a tyrosine kinase inhibitor protein for any other tyrosine kinase, (and thus the subject-matter of the claims is not sufficiently disclosed). Accordingly, if the subject-matter of claim does not solve the technical problem in its whole scope, but only for a particular case (c-Abl tyrosine kinase activity), the claim as a whole can not be considered to involve an inventive step.

Lack of clarity

5.4 **Furthermore, claims 1-27 and 31-54, which make reference to the cap region of c-Abl, are not clear**, contravening the requirements of Article 6 PCT.

According to the PCT Preliminary Examination Guidelines, the meaning of the terms of a claim should, as far as possible, be clear for the person skilled in the art from the wording of the claim alone. "Each claim should be studied by the examiner giving the words the meaning and scope which they normally have in the relevant art, unless in particular cases the description gives the words a special meaning, by explicit definition or otherwise. Moreover, if such a special meaning applies, the examiner should, as far as possible, require the claim to be amended whereby the meaning is clear from the wording of the claim alone" (see Guidelines, Chapter III, Section 4.2).

No prior art document (excluding D1, cited as a P,X document) made reference to the "cap region of c-Abl", and thus the skilled person has not enough guidance as to the meaning of such expression. In contrast, a particular sequence or particular positions of a known protein would be clear features.

Industrial applicability

5.5 For the assessment of the present claims 36-38 and 40 on the question whether they

are industrially applicable, no unified criteria exist in the PCT Contracting States. The EPO does not recognize as industrially applicable methods of treatment of the human body by surgery or therapy and diagnostic methods practised on the human or animal body. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.